

Breaking the Skin Barrier:  
Modelling Microneedles for Transdermal Insulin Delivery

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## 1. Executive Summary

Transdermal patches, devices developed to deliver drugs, can be limited in their efficacy because the amount of drug that diffuses through the skin often doesn't reach sufficient concentrations. This problem is alleviated by using the 'poke with patch' method, which uses a patch with microneedles to puncture the skin in order to help increase drug penetration through the skin.

In our project, we investigated varying number of punctures and modeled how that impacts drug diffusion through the skin over time. We modeled this system in COMSOL as a 2D slab representing the multiple layers within the skin, and simulated insulin flow from the patch into the capillary blood layer. To study the effect of the number of punctures on drug delivery, we created four models with 5, 10, 20, and 50 microneedle punctures. We then gathered data of insulin concentrations over 24 hours at two different points in the geometry—underneath a microneedle and at the exit of the blood domain—as well as in the drug patch and in the body. The data gathered from all four models were then evaluated to find the trends.

The data collected showed that as we increase the number of microneedles in the patch, the insulin concentration underneath the needle decreases. However, with a greater number of microneedles, the insulin concentration exiting the blood domain significantly increases, and insulin exits the drug patch at a faster rate.

From our results, we see that the addition of microneedle punctures improves the efficacy of transdermal patches by increasing the insulin delivered into the body through the patch. Since insulin concentration in the blood increases when there are more microneedles in the patch, we can conclude that increasing the number of microneedle punctures optimizes drug delivery. However, there should be a limit on the number of punctures to prevent potential clinical damage to the skin.

## 2. Introduction

### *Background*

In the United States alone, 29.1 million people have diabetes which translates to 9.3% of the country's population [1]. People are diagnosed with diabetes when their body cannot use or store glucose that is uptaken from food, either because the pancreas no longer makes insulin or the body does not respond to the insulin being made. Hyperglycemia defines when a body uses fats as an energy source in place of glucose due to lack of insulin. This can cause the body to enter into a state of diabetic coma. Hypoglycemia defines when a body has low levels of blood glucose due to high levels of insulin. People suffering from diabetes have to take insulin shots to provide their body with insulin, usually before a meal. Timely injections are important, as too low levels or too high levels of blood glucose can be life-threatening. However, many patients find these hypodermic injections to be painful and inconvenient.

New approaches to drug administration have been developed to deliver drugs into the skin using a patch, thereby bypassing challenges in patient compliance and discipline. Transdermal delivery from patches alone is sometimes difficult due to the low diffusivity of the skin's stratum corneum which acts as the outermost barrier. To address this problem, the

“poke with patch” method uses solid microneedles to poke the skin to increase skin permeability as a patch coated with a drug is applied [2]. In this way, the drug slowly diffuses through the micron size pores and into the body. Another advantage to microneedles is that human subjects reported them as feeling painless, due to the small needle diameter and surface insertion. Microneedles can be constructed out of many different types of materials, such as silicon, nondegradable polymers, and metals in a range of sizes. They can also be fabricated into arrays of different amounts of microneedles depending on what drug is being administered [3]. After pretreatment of microneedles the increased permeability of skin allows compounds as large as 100 nm in diameter, making transdermal drug delivery possible for vaccines, oligonucleotides, anesthetics, and other macromolecules such as insulin [4].

Due to the easy application and convenience of these microneedle patches, transdermal drug delivery offers a viable alternative to diabetics who need insulin. This new innovative way of drug administration is currently still in clinical trials, however studies have been done to show that blood glucose levels have been lowered after the usage of microneedles to deliver insulin to diabetic mice [5].

### *Literature Review*

One study designed and fabricated microneedle arrays to deliver insulin to hairless, diabetic rats in vivo to see the effectiveness of lowering blood glucose levels. Arrays of solid, stainless steel microneedles were inserted into the skin of the rat’s lower back. A glass chamber was then attached to the site of puncture containing insulin and kept in contact to the rat’s skin for 4 hours. The rat’s blood glucose was then monitored and measured. The effects of insulin concentration, needle insertion time, and number of insertions were studied. They found that higher concentration lead to a greater reduction in blood glucose. A shorter microneedle insertion time yielded larger drops in blood glucose. A longer insertion time could block the holes, preventing the diffusion of insulin. More insertions also lead to a lower reduction in blood glucose, since this could damage the skin. This study showed the effectiveness of using microneedles for transdermal insulin delivery and optimized the method of drug administration in mice [5]. Currently, clinical trials are testing the efficacy and safety of transdermal insulin delivery through microneedles and patches in humans.

### **3. Problem Statement**

Transdermal drug delivery has been an effective technique for delivering medication, however this technique is limited by the efficiency at which the drug can diffuse through the skin. To increase skin permeability microneedles can be added to the patch, but too many will lead to skin damage. The purpose of our research is to understand how increasing the number of microneedles correlates to an increased drug delivery to the bloodstream, and compare those results to the amount delivered by insulin injection. Additionally, limiting the number of microneedles is important so as to not damage the skin.

Below is the list of assumptions used in modeling the insulin patch on COMSOL. These assumptions are applied to simplify the computation and simulate an ideal situation.

Assumptions:

1. Convective fluid flow in the needle is negligible because diffusion is the main source of mass transport.

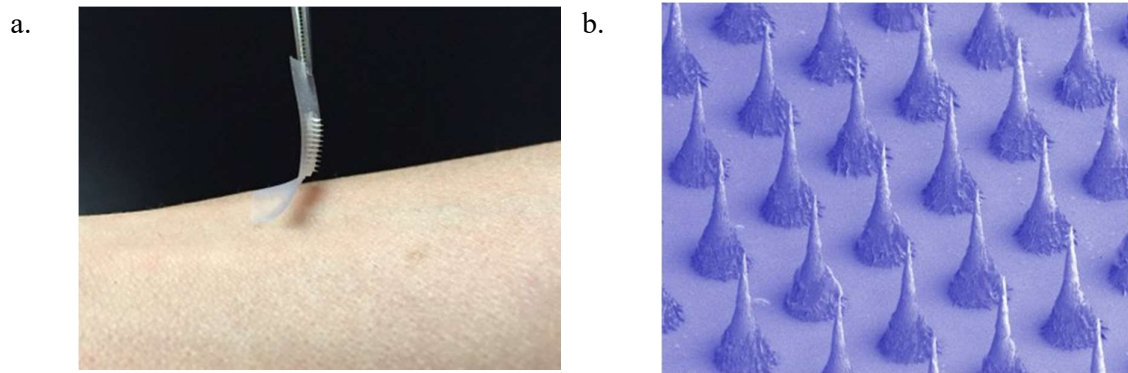
2. Pressure from applying patch will not affect the diffusion of drug delivery in the skin.
3. Dimensions of microneedle will remain constant.
4. Insulin will diffuse into the skin, from the microneedle, at the same rate over the entire surface of the microneedle.
5. The presence of hair on skin is ignored.

#### 4. Design Objectives

In this project, we will model the mass transfer of insulin through the skin as a 2D slab using the “poke with patch” method and study insulin delivery through the patch with 5, 10, 20, and 50 microneedle punctures. Concentrations of insulin will be investigated over 24 hours at two points: under a microneedle and at the exit of the blood domain. We will also study how insulin concentration changes in the body over the same amount of time and observe how the number of microneedles affects the rate at which insulin is depleted from the patch. The goal is to determine the optimal number of microneedles to maximize drug delivery and to compare the “poke with patch” method with insulin delivery through injection.

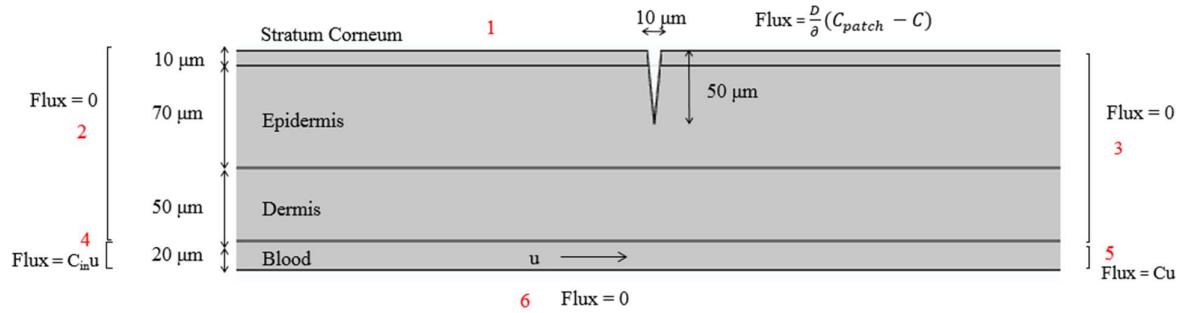
#### 5. Schematic

Insulin patches have been designed and are currently being tested. One type of patch that has been invented is the Smart Insulin Patch by University of North Carolina and North Carolina State [6]. Microneedles protrude out of the patch and contain insulin that release it into the skin.



**Figure 1. Smart Insulin Patch.** (a) Patch being placed on skin. (b) Electron microscopic view of the microneedles on the patch. [6].

We have simplified this design to model mass transfer. Figure 2 below takes a closer look at one microneedle of the entire insulin patch. The schematic is a 2D illustration of the skin and blood domain after the microneedles have punctured through the skin. There are four domains: stratum corneum, epidermis, dermis, and blood. The entire patch is 2 cm wide, and the needles are spaced evenly throughout. The needles are organized into arrays with a variable number of needles per row. The dimensions of the skin domain and needles were found from literature research.



**Figure 2. Schematic of one microneedle in model.** A 2D schematic of one section of the insulin patch with one microneedle puncture. The model consists of two different domains: the skin (stratum corneum, epidermis and dermis) and blood. The boundary labels are shown in red.

The spacing between each needle is changed in order to optimize the number of microneedles in a patch. Number of needles modeled were 5, 10, 20, and 50. The first and the last needles on every patch were placed 1.179 mm from the edge and were evenly spaced across the patch. Figure 3 below shows diagrams of the leftmost 6 mm of each patch.

a. 5 needles, spacing of 4.11 mm



b. 10 needles, spacing of 1.82 mm



c. 20 needles, spacing of 0.864 mm



d. 50 needles, spacing of 0.335 mm



**Figure 3. Schematic of different needle spacings.** Figures (a)-(d) show patches with increasing number of microneedles in each patch. The first and last needles on each patch are lined up.

From Figure 3, we can see that as the number of microneedles increases, the spacing between each needle decreases. We tested no more than 50 microneedles per array because of potential cosmetic damage to the skin.

## 6. Governing Equations

The following equations are the vector notation form of the mass transfer equations of the

stratum corneum, epidermis, and dermis domains:

$$\frac{\partial C}{\partial t} = D_{SC} \nabla^2 C \quad (1)$$

$$\frac{\partial C}{\partial t} = D_E \nabla^2 C \quad (2)$$

$$\frac{\partial C}{\partial t} = D_D \nabla^2 C \quad (3)$$

where  $C$  is the concentration of insulin in the skin,  $D_{SC}$ ,  $D_E$ , and  $D_D$  are the diffusivity constants in the stratum corneum, epidermis, and dermis, respectively. We assumed that there is no consumption or degradation of insulin in the skin; therefore there is no reaction term. In this governing equation, the convective term has been dropped since mass transfer is only due to diffusion.

These are the governing equations for the blood domain, again in the vector notation form of the continuity equation, laminar flow, and mass transfer equation:

$$\frac{\partial \rho}{\partial t} + \nabla(\rho \mathbf{u}) = 0 \quad (4)$$

$$\rho \frac{\partial \mathbf{u}}{\partial t} + \rho \mathbf{u} \nabla \mathbf{u} = \mu \nabla^2 \mathbf{u} \quad (5)$$

$$\frac{\partial C}{\partial t} + \mathbf{u} \nabla C = D_{blood} \nabla^2 C \quad (6)$$

where  $C$  is the concentration of insulin in the blood,  $\mathbf{u}$  is the blood velocity vector,  $D_{blood}$  is the diffusivity constant of insulin in the blood,  $\rho$  is the density of blood, and  $\mu$  is the viscosity of blood. Equation 4 is the continuity equation and solves for no pressure in the fluid flow. Equation 5 represents laminar flow in the blood and equation 6 represents the mass transfer of the insulin through the blood domain, which is affected by convection and diffusion.

### *Ordinary Differential Equations*

These are the ordinary differential equations for the patch domain used to define boundary conditions:

$$F = -n \cdot (-D \nabla c) \quad (7)$$

$$\dot{m} \left[ \frac{kg}{time} \right] = L \int_0^L F \, dx \quad (8)$$

$$V_{patch} \cdot \frac{dC_{patch}}{dt} = -\dot{m} \quad (9)$$

$$F = \frac{D}{\delta} (C_{patch} - C) \quad (10)$$

where  $F$  is the flux, the rate at which drug is leaving the patch, and  $n$  is the normal vector to the surface.  $\dot{m}$  is the mass lost from the patch with respect to time.  $C_{patch}$  is the concentration of blood in the patch, initially at  $C_{patch,0}$ .  $D$  is the diffusivity value of the drug in the patch. The opposite of mass lost from the patch is equivalent to the mass gained in the skin which is represented by equation 9.

This is the ordinary differential equation in the blood domain:

$$V_{blood} \frac{dC_{body}}{dt} = L \int_0^h \mathbf{u} \cdot \mathbf{c} \, dy - KV_{body}C_{body} \quad (11)$$

where  $C_{body}$  is the concentration of insulin inside the body, where there is consumption and degradation, and is equivalent to  $C_{in}$ .

## 7. Model Implementation

### *Boundary Conditions*

All boundary conditions are labeled at their respective boundaries as shown in Figure 2.

#### *Boundary 1:*

The needle/patch boundary where insulin diffuses into the skin domain consists of the entire top surface including the punctures created by the microneedles. Initially, this boundary has a concentration of  $C_{patch,0}$ , and decreases as the drug leaves the patch and enters the skin. Therefore, this boundary has a flux condition that is calculated taking into account the diffusivity of the drug through the patch, and how much drug is left in the patch.  $C_{patch,0}$  was decided by the concentration of insulin given in injections. The concentration entering the skin domain decreases over time and is modeled by equations 8 and 9.

#### *Boundaries 2 and 3:*

This project only models the diffusion of insulin into the skin and capillary from the needle/patch boundary. Therefore, there is no drug diffusing out of the boundaries in the x-direction. These boundaries were set to have no flux.

#### *Boundary 4:*

Blood is entering the blood domain and is therefore given the flux equal to  $C_{in}\mathbf{u}$  where  $C_{in}$  is the concentration of insulin in the blood coming into the domain and  $\mathbf{u}$  is the blood velocity. The expression for  $C_{in}$  is equal to  $C_{body}$  and is given in equation 11, and models how some insulin is consumed while it travels through all the blood in the body before returning to the model's domain.

#### *Boundary 5:*

This boundary has a flux condition, where flux is  $C\mathbf{u}$  where  $C$  is the insulin concentration in the blood when it leaves the domain. The insulin concentration here is affected by the diffusion of drug from the top surface, fluid flow, and the concentration of drug already in the blood over time.



*Boundary 6:*

The blood is flowing all of the insulin out of the domain into the body. Therefore there is no flux at this boundary.

*Initial Conditions:*

Initially there is zero drug in all domains.

*Parameters*

The following table shows the values that we used to accurately model the problem taken from literature research, estimation, and assumptions.

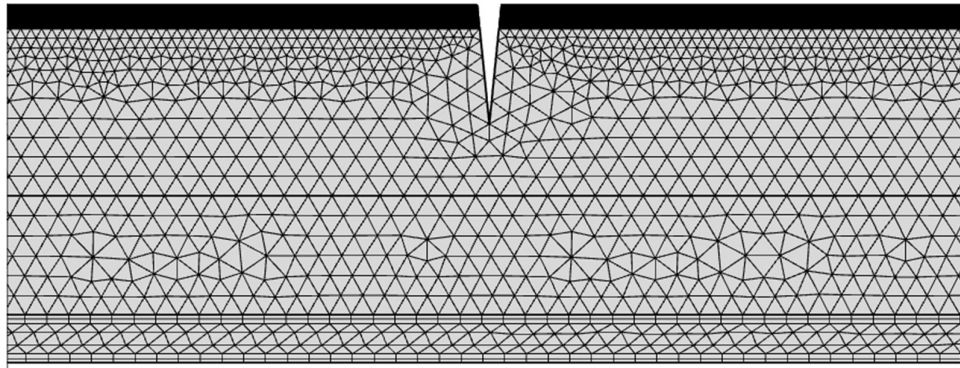
**Table 1. Parameters.** A list of parameters use in the COMSOL model.

Parameter	Value	Source
Diffusivity in Stratum Corneum ( $D_{sc}$ )	$3.97 \times 10^{-16} \text{ m}^2/\text{s}$	[7]
Diffusivity in Epidermis ( $D_E$ )	$1.58 \times 10^{-13} \text{ m}^2/\text{s}$	[8]
Diffusivity in Dermis ( $D_D$ )	$5.8 \times 10^{-11} \text{ m}^2/\text{s}$	[8]
Initial Insulin Patch Concentration ( $C_{patch,0}$ )	0.6198 mol/L	[4]
Capillary Blood Velocity ( $u$ )	$4.7 \times 10^{-4} \text{ m/s}$	[9]
Viscosity of Blood ( $\mu$ )	2.78 mPa s	[10]
Density of Blood ( $\rho$ )	1060 kg/m <sup>3</sup>	[11]
Volume of Blood ( $V_{body}$ )	5 L	[12]
Thickness of Insulin Patch ( $\delta$ )	1 mm	
Length of Patch ( $L$ )	2 cm	
Volume of Patch ( $V_{patch}$ )	$4.0 \times 10^{-7} \text{ m}^3$	

## 8. Results

### *Mesh*

Figure 4 below shows the meshing of the skin and blood domain model. This meshing is the final converged mesh made with mapped distribution and free triangular elements. The figure shows extremely fine meshing in the stratum corneum layer and increasingly coarser mesh towards the dermis and blood domain. The appearance of the stratum corneum domain as a black solid indicates a very fine mesh.



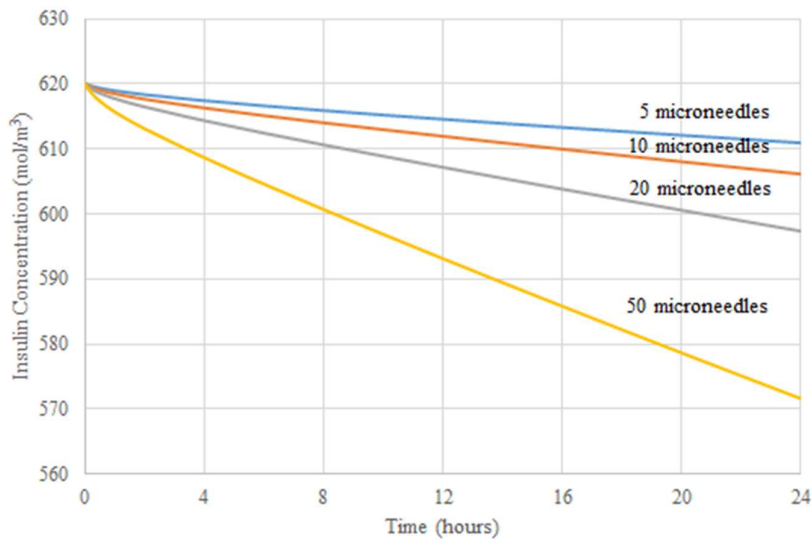
**Figure 4. COMSOL mesh.** This mesh has a mapped distribution in the stratum corneum and free triangular mesh on the other domains of the skin. There are 392949 total elements.

The finer mesh in the stratum corneum shown above allows more accurate calculations of the concentration of insulin exiting the microneedles.

### *Solution*

For all the different number of microneedles in the patch, we evaluated the concentration of insulin at a point under a microneedle in the blood domain, at the outlet of the blood domain, in the patch, and in the body over 24 hours. These graphs are shown below in Figures 6 through 9 respectively.

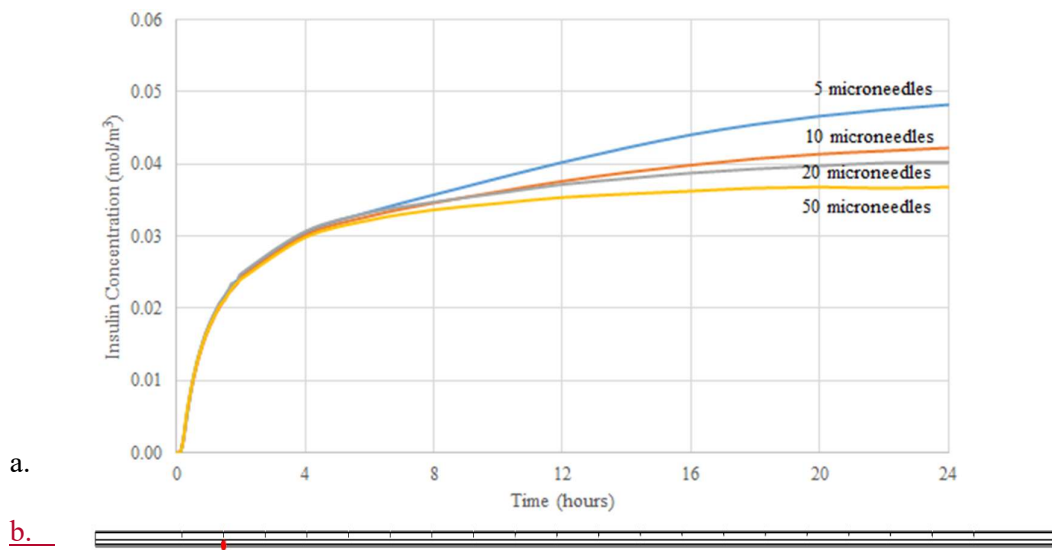
The following figure shows how the amount of insulin in the patch decreases over time.



**Figure 6. Insulin concentration in the patch.** The change in insulin concentration over 24 hours in the insulin patch.

In Figure 6, insulin concentration in the patch decreases after the patch is applied and drug begins to diffuse into the skin domain. Patches with more microneedles decreased in concentration much faster, because more drug is entering the skin due to increased permeability caused by the greater number of punctures.

The insulin concentration was measured under the second microneedle of every patch to look at the effect of the diffusion of the drug through the layers of skin before being carried away by the blood flow.

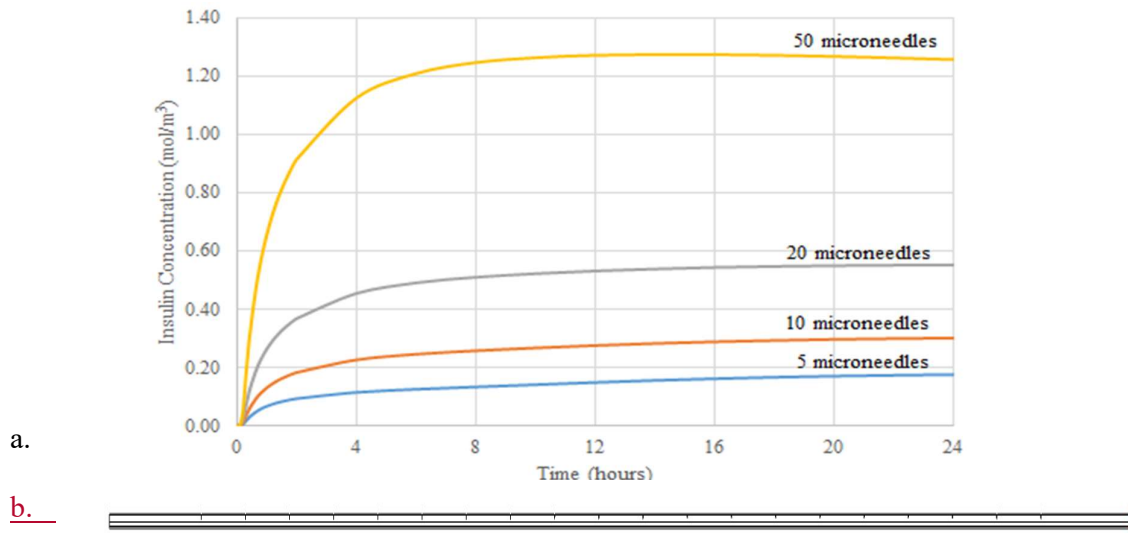


**Figure 7. Insulin concentration under a needle.** (a) The change in insulin concentration over 24 hours at a point under the second microneedle of all four patches. (b) The position of the cut point on the model with 20 microneedles.

Figure 7 shows the sharp increase in insulin concentration when the patch is first applied, then a gradual increase after 4 hours. Fewer microneedles resulted in higher concentrations of

insulin. This trend occurs because each model begins with the same amount of insulin, and if there are less punctures for the insulin to diffuse through, a greater amount would diffuse through each needle.

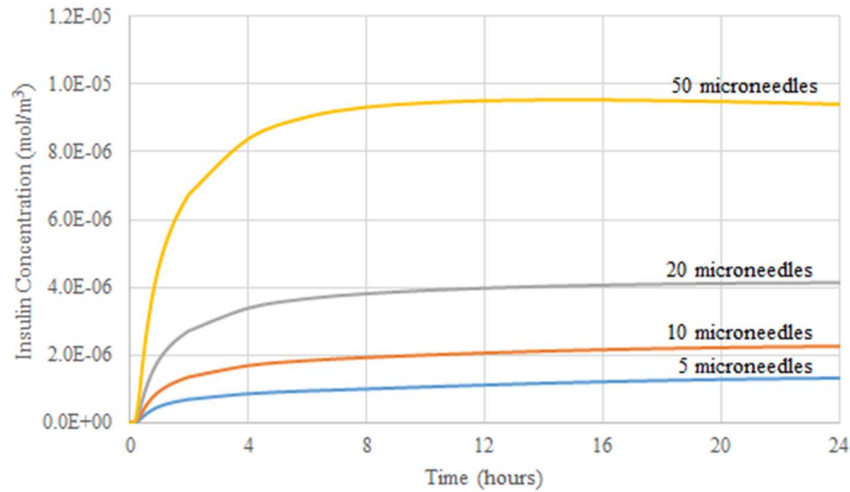
Concentration of drug was also measured at the blood domain exit boundary, which shows both the effect of drug diffusion through the skin from the needles and from fluid flow.



**Figure 8. Insulin concentration in blood domain exit boundary.** (a) The change in insulin concentration over 24 hours at a point at the exit boundary of the blood domain. (b) The position of the cut point on the model with 20 microneedles.

As seen in Figure 8, the concentration of insulin at this point is greatest for the 50 microneedle model and the least for the 5 microneedle model. Due to increased permeability of the skin, more drug is able to enter the domain in the 50 microneedle patch; therefore, more drug exits the blood boundary and enters the body.

In order to determine the efficacy of insulin delivery into the body, the concentration of insulin was measured over 24 hours in the body. The insulin is traveling through the entire body's bloodstream and is also being consumed.

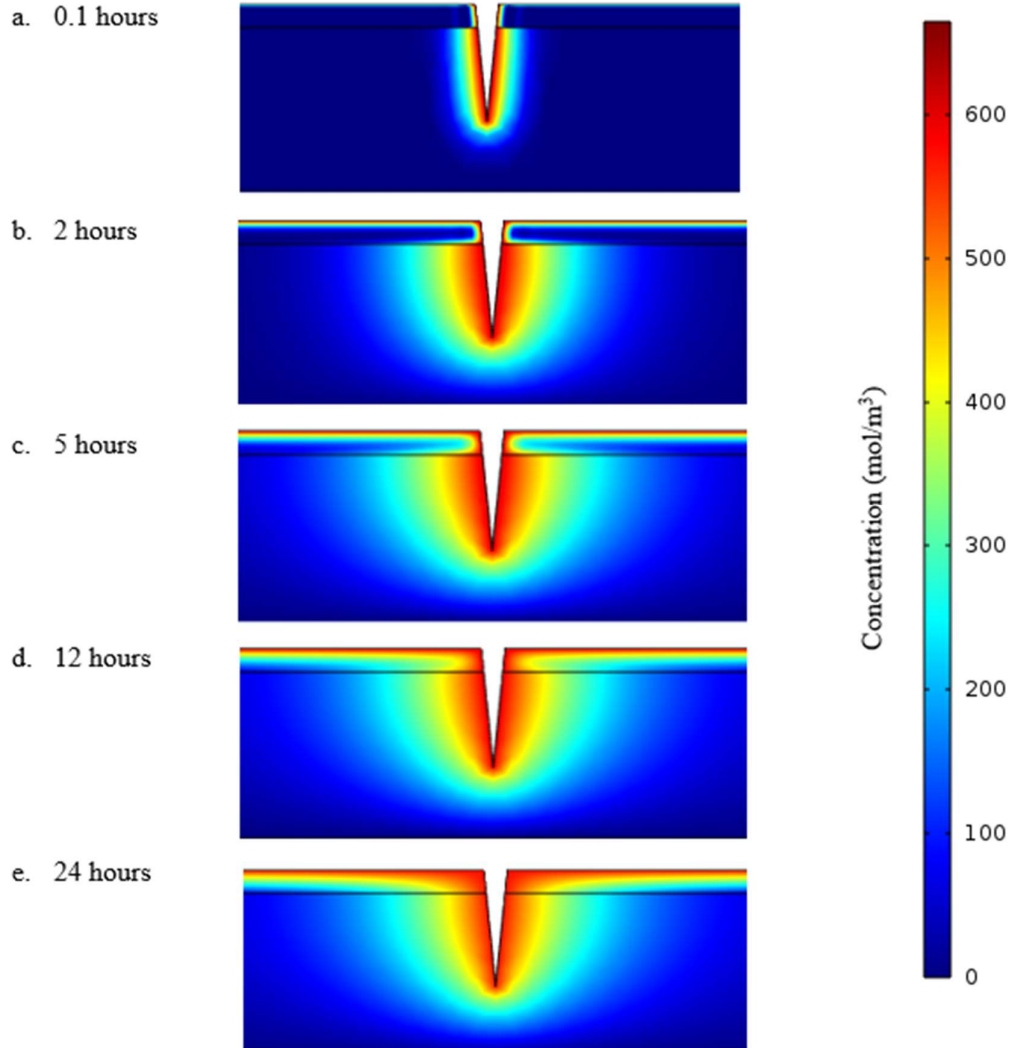


**Figure 9. Insulin concentration in the body.** The change in insulin concentration over 24 hours in the body.

Similar to the trend of the previous plot, Figure 9 shows that the 50 microneedle patch delivers the greatest amount of insulin into body. A greater number of microneedles allows more drug to diffuse through the skin, into the blood, and into body. The concentration plateaus because there is limit to the amount of drug that can enter the skin and blood from each material's diffusivity.

Figure 10 shows five surface plots of insulin concentration in the model at 0.1, 2, 5, 12, and 24 hours. These times were chosen to depict how the insulin diffuses through the stratum corneum and epidermis over 24 hours. The dermis and blood domains are not shown in these surface plots in order to focus on the diffusion of insulin at a microneedle.

**Time after patch applied**



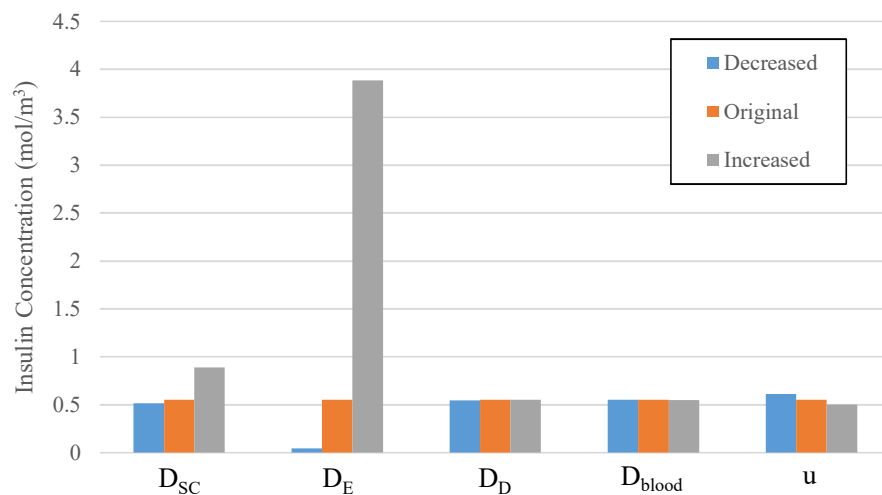
**Figure 10. Surface plot of insulin.** Plots a- e show surface plots of the 50 microneedle patch model at times 0.1, 2, 4, 12, 24 hours, respectively.

Figure 10a shows the insulin concentration at 0.1 hours. The stratum corneum has very low diffusivity, and so insulin diffuses through this top layer at a much slower rate than in the epidermis. Throughout time, the concentration at the needle will decrease as the amount of insulin in the patch is slowly depleted. Figure 10b illustrates that at 2 hours, most of the drug is still mainly diffusing through the epidermis but not the stratum corneum. After 5 hours, more insulin is diffusing through the stratum corneum, as shown in Figure 10c. The amount of insulin diffusing through the epidermis at 5 hours is now limited by the diffusivity of the epidermis since the surface plot of the epidermis does not change significantly in later times. Figure 10d shows the low diffusivity of the stratum corneum, since there are still regions with no drug present at 12 hours. Most of the drug is diffusing through the punctures into the epidermis. Figure 10e shows that by 24 hours, the starting amount of insulin in the patch hasn't been completely depleted.

## 9. Discussion

### *Sensitivity Analysis*

For sensitivity analysis, we looked at the effect of a few of our parameters to see the importance in the overall model. The values we used for the diffusivities of insulin in the stratum corneum, epidermis, dermis, and blood were based on literature and also estimations. Varying these parameters by powers of ten shows the need for accuracy for certain aspects of our model. The blood velocity was also changed by 10% to take into account differences in how active the patient is, where the patch is applied, and the age of the patient. The concentration of insulin at 24 hours at the blood domain exit was chosen to be the point of measurement, because this location and time will show the compiled effects of drug diffusion and fluid flow through the model.



**Figure 12. Sensitivity Analysis.** Changes in modeled insulin concentration after 24 hours at blood exit boundary. Diffusivities were increased or decreased by powers of ten for diffusivities and by 10% for blood velocity.

As shown in Figure 12, there is a very drastic change in insulin concentration when varying the diffusivity of the epidermis and a slight change in insulin concentration when varying the diffusivity of the stratum corneum. Our model is extremely sensitive to changes in the diffusivity of the epidermis, because this skin layer has the largest impact on the diffusion of the drug through the domain. The epidermis is the thickest layer of skin in our modeled domain, and the drug from the puncture directly enters into the epidermis. There was almost no effect when varying the diffusivity of the dermis and blood. This illustrates how the diffusion of the drug through the dermis and blood are not the main components of mass transfer.

Sensitivity analysis on the blood velocity was tested on values 10% slower and 10% faster than the original value of 0.47 mm/s. As Figure 12 shows, increase in the blood velocity decreases the concentration of insulin drug at the blood domain exit. This is because with a faster velocity, more of the drug is being carried away out of the examined domain into the rest of the body. The model is not very sensitive in changes in the blood velocity.

## *Conclusion*

Of our models, the one with 50 microneedles delivered the most amount of insulin to the body, due to the increased permeability of the skin with more microneedle punctures. Lantus, a market brand of insulin, recommends 10 units of insulin per day which translates to  $0.124 \mu\text{mol}/\text{m}^3$  [13]. After 24 hours, our 50 microneedle model led to a body concentration very close to this value at  $0.0941 \mu\text{mol}/\text{m}^3$ . This is the concentration resulting from one array of 50 microneedles. A realistic patch in 3D would contain many arrays which will deliver a greater concentration of insulin to the body. This makes the patch more efficient at delivering insulin to the body than insulin injections, saving costs. In addition, transdermal patches are more convenient and less painful, making it an attractive alternative to the traditional hypodermic injections.

## *Validation*

Microneedle arrays have been optimized to increase skin permeability for transdermal drug delivery. Permeability of skin was plotted, changing the number of microneedles, as an optimization function. The study determined that the ratio of surface patch of the area to needle should be smaller for a more optimal drug delivery [14]. This is also what we found in our model; there was greater drug delivery (higher drug concentration in the skin or body) in patches with more microneedles, as seen in Figures 6, 8, and 9.

Compared to the study of transdermal delivery of insulin using microneedles into hairless, diabetic mice, our model had similar values of the concentration of insulin in the body. The concentration of blood insulin inside the mice immediately after the insulin delivery period were  $0.5\text{--}7.4 \text{ ng/mL}$ . This is equal to an insulin concentration of  $9 \times 10^{-8} - 1.27 \times 10^{-6} \text{ mol}/\text{m}^3$ . Our value of  $C_{\text{body}}$  is within that range for 5 microneedles. This is largely due to the simplicity of our model. In real life, there are many other things that can affect the diffusion of insulin from the patch into the skin, and the consumption of insulin in the body. The reduction in blood glucose determined the effectiveness of the insulin microneedles [5]. Unfortunately, this is not possible to determine in our model, since how the body uses insulin to reduce blood glucose is difficult to calculate and depends on more factors than just insulin concentration.

## *Future Work*

Our results have shown that using insulin patches with microneedles are effective in efficiently delivering insulin into the body. However, our simulation is simplified in that it only used diffusion and fluid flow to model the mass transfer. In a real patient, there are many more factors that affect the delivery of insulin, including consumption and degradation in the body. Though the concentration of insulin fits the recommended dosage, we are unaware of the glucose levels in the body. It was also assumed that the microneedles are not painful and that a patch with more than 50 microneedles could cause cosmetic damage. Consequently, human trials are essential to evaluate the efficacy of insulin patches with microneedles.

The microneedle patches can be made with materials easily found and commonly used in cosmetic products [5]. Transdermal patches like nicotine patches, already exist in the market. Therefore, production of insulin patches will be easily feasible once clinical trials show its effectiveness.

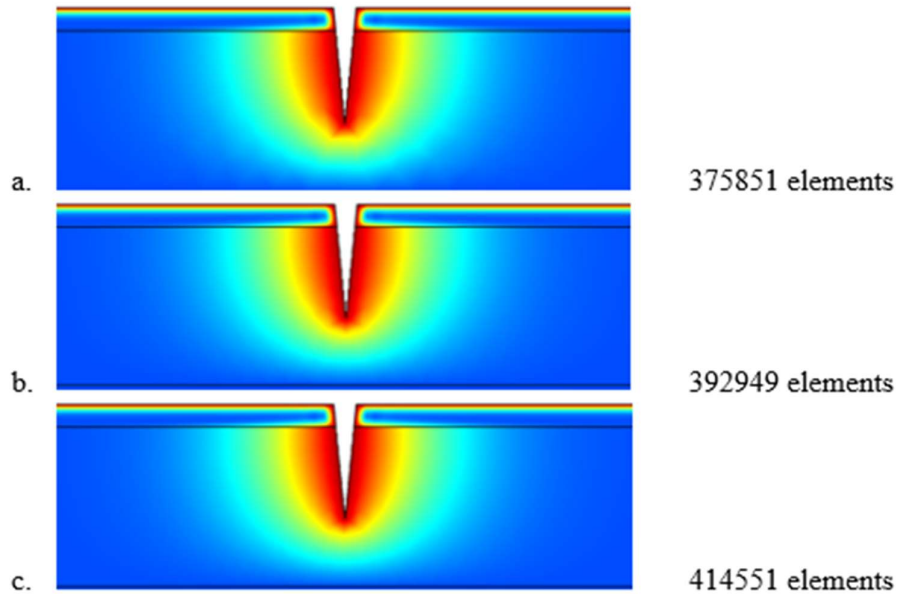
Transdermal drug delivery provides an appealing new alternative to inconvenient and painful insulin injections for diabetic patients.



## 10. Appendices

### *Mesh Convergence*

In order to have COMSOL accurately calculate the concentration of insulin in our model, we performed a mesh convergence by visually observing the concentration surface plot near 1 needle at 3 hours. The only domain that needed mesh convergence was the epidermis domain because that is the area where the drug diffuses out of the needle. We found that the mesh converged when there were 392949 elements.



**Figure 11. Mesh Convergence.** Surface plots around one microneedle when the mesh has (a) 375851 elements, (b) 392949 elements, and (c) 414551 elements.

There was a slight change in the concentration surface plot from Figure 11a to 11b, which indicated that the mesh was not completely converged. So we made the elements even smaller to obtain the surface plot in Figure 11c. Since this plot showed little difference from Figure 11b, we concluded that the mesh was converged at 392949 elements.

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